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REVIEW

Role of epigenetic reprogramming of host genes in bacterial pathogenesis

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Abstract The genomes are regularly targeted by epigenetic regulatory mechanisms (DNA methylation, histone modifications, binding of regulatory proteins) in infected cells. In addition, proteins encoded by microbial genomes may disturb the action of a set of cellular promoters by interacting with the same epi-regulatory machinery. The outcome of this may result in epigenetic dysregulation and subsequent cellular dysfunctions that may manifest in or contribute to the development of pathological changes. How epigenetic methylation decorations on DNA and histones are started and established remains largely unknown. The inherited nature of these processes in regulation of genes suggests that they could play key roles in chronic diseases associated with microbial persistence; they might also explain so-called hit-and-run phenomena in infectious disease pathogenesis. Microbes infecting mammals may cause diseases by causing hyper-methylation of key cellular promoters at CpG di-nucleotides and may induce pathological changes by epigenetic reprogramming of host cells they are interacting with elucidation of the epigenetic consequences of microbe–host interactions may have important therapeutic implications because epigenetic processes can be reverted and elimination of microbes inducing patho-epigenetic changes may prevent disease development.

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1. Introduction

Epigenetics has been defined as the study of stable alterations in gene expression potentials that arise during development and cell proliferation (Jaenisch et al., 2003), or alterations in DNA function without alterations in DNA sequence (Jones and Takai, 2001). In 1942, Waddington first introduced the concept of epigenetics (Waddington, 1942) by describing the influence of environmental factors on the development of specific traits through gene-environment interaction. Waddington's words "the interaction of genes with their environment, which bring the phenotype into being" are the key to developmental biology, i.e. the "idea that phenotype, or the morphologic and functional properties of an organism, arise sequentially under a program defined by the genome under the influence of the organism's environment" (Van Speybroeckm, 2002). Modern aspects of epigenetics refer to the modification of DNA and/or related proteins without variation in nucleotide sequences, which passes the contained information to next generation (Fig. 1). It has been thought that diseases are mainly driven by acquired genetic changes. Now, it is becoming clear that any phenotype is the result of complex interactions between genotype, epi-genome, and environment. Epigenetics focuses on processes that regulate how and when certain genes are turned on and/or off, while epi-genomics analyzes epigenetic changes across many genes in a cell or entire organism. For decades epigenetics is considered to be at the epicenter of modern medicine since it helps to explain the relationship between individual genotype and the environment during all stages of living beings and perturbations in epigenetic mechanisms that can result in various health disturbances (Feinberg, 2008). Epi-genomic reprogramming of cell genome and post-translation modification of gene expression are essential mechanisms of the development, regeneration, and postnatal life of higher organisms (Choudhary et al., 2009; Tollefsbol, 2010). Human epigenetics may explain some features of various monogenic and multifactorial disorders as well as their late onset, gender effects, fluctuation of symptoms, phenotypic differences between monozygotic twins and others. Epigenetic code can be individual as well as tissue- and cell-specific and may change over time because of aging, disease, or environmental factors and other agents. Epigenetics does not involve an alteration in the nucleotide sequence of the DNA; epigenomic effects are connected with the covalent attachment of different chemical groups to DNA, chromatin, histones, and other associated proteins during post-translation period. DNA and histone methylation, acetylation, biotinylation, phosphorylation, ADP-ribosylation, repeat-induced gene silencing, miRNA interferences, ubiquitination, sumoylation, genomic imprinting, and so on are few examples of epigenetics. Epigenetic DNA and chromatin alterations persist from one cell division to the next and can occur for several cell generations (Feinberg, 2008; Tollefsbol, 2010; Furrow et al., 2011). In body fluids methylated DNA, acetylated proteins, miRNA, specific substrates, cofactors, enzymes participating in the biochemical reactions connected with epigenomics processes could be biomarkers for detecting some metabolic diseases (Casadesus and Low, 2006; Martens et al., 2009; Qureshi et al., 2010).

1.1. Epigenetic modifications induced by microbial invasion

Several studies have shown that certain infectious agents (*Helicobacter pylori, Streptococcus bovis, Chlamydia pneumoniae, Campylobacter rectus, Epstein-Barr* virus, hepatitis viruses, Human papilloma virus, polyomaviruses, etc.) can contribute

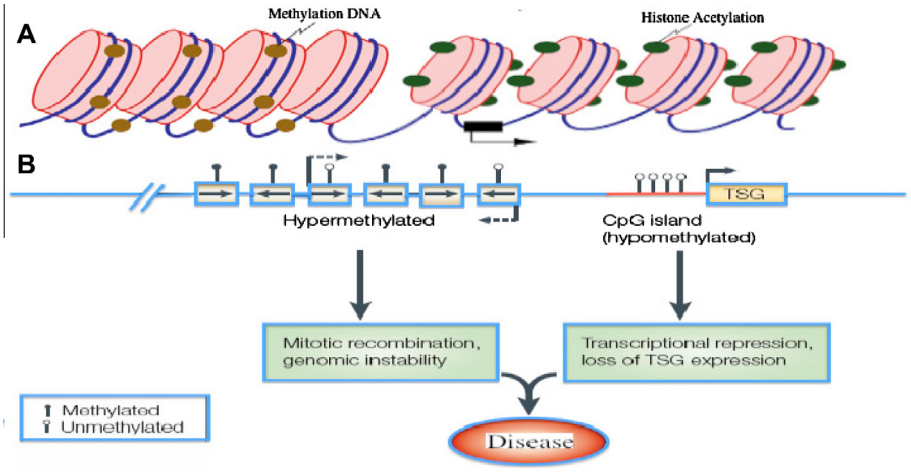

Figure 1 The figure shows a representative region of genomic DNA. Methylation of cytosine residues is associated with gene silencing. Methylation of certain genomic regions is inherited (imprinting) and is involved in the silencing. Alterations in methylation can also be acquired (e.g. in cancer cells). The region contains repeat-rich, hyper-methylated heterochromatin and an actively transcribed tumor suppressor gene associated with a hypo-methylated CpG island (indicated in red).

Table 1 Examples of few microbe-induced epigenetic dysregulations.

Microbe	Mode of action	Effects
Campylobacter rectus	Methylation of igf2 promoter region	Silencing of Igf2 P0 promoter by CpG methylation in the placenta
Helicobacter pylori	Polycomb-repressive marks pinpoint the promoters to be silenced	Silencing of selected promoters by CpG methylation
Epstein-Barr virus	Up-regulation of DNMT1, 3A, 3B via the JNK-AP-1 pathway	Silencing of E-cadherin promoter
Human adenovirus	Stimulation of E2F activity, up-regulation of DNMT1; association with DNMT1, stimulation of DNMT1 activity	Dysregulation of DNMT1, 3A, 3B
Human papillomavirus	Association with DNMT1, stimulation of DNMT1 activity; increasing histone acetylation	Activation of E2F and CDC25A promoters
Hepatitis B virus	Up-regulation of DNMT1 via the cyclin D1-CDK4/6-pRb-E2F1 and p38MAPK pathways; up-regulation of DNMT3A1 and DNMT3A2; Down-regulation of DNMT3B	Silencing of tumor suppressor genes

to the host epigenetic changes resulting in the onset and progression of some diseases, especially in malignancies. Few examples of microbe induced host gene methylations are in Table 1. The symbiotic microorganisms have been implicated in epigenetic thermotolerance variation of coral reef cnidarian symbiosis, pea aphids, and cactuses (Gilbert et al., 2010). A role of mammalian gut microbiota, as epigenetic modifying factor, in the pathogenesis of metabolic syndrome and associated diseases has been meant (Dumas et al., 2006). Thus, the different biotic and abiotic signals can produce changes in gene expression that can persist after the effect has ceased (Oka et al., 2011, Paschos and Allday, 2010). However, the epigenomic reprograming and post-translated molecular mechanisms connected with symbiotic microflora remain unclear. Through the analysis of different microbial molecules, the role of gut indigenous microbiota in epigenomic mechanisms and the consequences of gut micro ecological imbalance and epigenetic abnormalities in the onset and progression of diseases are associated (Murata et al., 2007; Alvarez-Venegas et al., 2007).

Microbial manipulation of host epigenetic marks as obligate intracellular parasites has helped develop numerous ways of hijacking cell processes to facilitate the completion of their life cycle and sometimes to evade the immune responses of their host. Microbes that cause persistent infections are likely to benefit from heritable epigenetic changes in host transcription that produce an environment for their latent or persistent state without having to continuously express the initiating effectors (Virgin et al., 2009). Host genes involved in cell cycle progression, senescence, survival, inflammation and immunity are prime candidates as targets for such epigenetic control. Some chronic bacterial infections are also associated with malignancy, the most and widely studied being *Helicobacter pylori* infection of human gastric mucosa. Moreover, many microbes have evolved ways of eluding the immune response and, again, epigenetic changes in host cells have been implicated in these processes. Viral infection can deregulate patterns of repressive histone modifications that could then precipitate aberrant DNA methylation and the reprograming of infected cells and their progeny. This can engage the repression of tumor suppressor genes, for which there will be a strong selection in the development in cancer. Infection by diverse microbes appears to induce expression of DNA methyl transferases (DNMTs) and/or polycomb group (PcG) proteins such as EZH2. The important caveat is that the expression of DNMTs and EZH2 correlates with cell proliferation rate; therefore a high level of expression might be a consequence of the proportion of cells proliferating in tumors and/or chronically inflamed tissue (Murata et al., 2007; Alvarez-Venegas et al., 2007). The first step in any epigenetic study is global DNA methylation analyses which allow the detection and identification of DNA methylation. These approaches do not require previous knowledge of the genome of reference, and most rely on a prior enzymatic/chemical hydrolysis of DNA to obtain 2′-deoxymononucleosides, followed by the subsequent separation by chromatographic means such as *High Performance Liquid Chromatography* (HPLC) (Eick et al., 1983) or *High Performance Capillary Electrophoresis* (HPCE) (Fraga et al., 2000), and a final detection step by UV spectroscopy or mass spectrometry. Alternatively, the global content of DNA methylation can also be quantified by enzymatic approaches such as the *Luminometric Methylation Assay* (LUMA) (Karimi et al., 2006). DNA methylation refers to the addition of a methyl group to the cytosine bases of DNA to form 5-methylcytosine. DNA methylation occurs in both prokaryotes and eukaryotes. In bacteria, DNA methylation differentiates the genome DNA from invading phage DNA, so that phage DNA is cleaved by the host restriction enzymes (Chinnusamy and Zhu, 2009).

Most epigenetic systems known in bacteria use DNA methylation as a signal that regulates a specific DNA–protein interaction. These systems are usually composed of a DNA methylase and a DNA binding protein(s) that bind to DNA sequences overlapping the target methylation site, blocking methylation of that site. Methylation of the target site, in turn, inhibits protein binding, resulting in two alternative methylation states of the target site, methylated and non methylated. The epigenetic modifications induced by infecting bacteria in multicellular eukaryotes seem to be mediated by mechanisms unrelated to the transfer of bacterial restriction-modification systems, and represent a novel research field to be explored. Some studies described that *Campylobacter rectus*, involved in periodontal infections and associated with an increased risk of pre-term births due to placental and fetal infection in humans, could induce, in infected mice, hyper-methylation in the promoter region P0 of the Igf2 (insulin-like growth factor 2) gene in the placenta (Berger et al., 2009; Meissner, 2010), and concluded that the intra-uterine growth restriction they observed in Campylobacter rectus infected animals was a consequence of the epigenetic alteration induced by the bacterial infection in the murine placenta.

1.2. Pathogen-induced alterations of the host

In the past, the term ''epigenetics'' has been used to describe the differentiation of genetically identical cells into distinct cell types to form tissues and organs during development of a multicellular organism. In current practice the word is used by biologists to describe heritable changes in gene expression that occur without changes in the DNA sequence. In the strict sense, epigenetic systems involve two or more heritable states, each maintained by a positive feedback loop. In a broader sense, however, any additional information superimposed to the DNA sequence (e.g., methylation of DNA) can be considered ''epigenetic (Josep and David, 2006). Pathogen-induced alterations of host physiology, morphology, and behavior are widely documented in the scientific literature. Perhaps the most fascinating examples of these changes are those that have been shown to be the result of a manipulative strategy of the pathogen aimed at maximizing its survival and transmission. In the last few years, however, evidence has accumulated that histone modifications and chromatin remodeling regulate gene expression and are thus key targets for pathogen manipulation during an infection (Hamon and Cossart, 2008). One such obvious target is host's immune system. In recent years, the epigenetic modulation of host's transcriptional program linked to host defense genes has emerged as a relatively common occurrence of pathogenic viral and bacterial infections (Paschos and Allday, 2010). Bacteria are the hallmark of epigenetic studies on microbes and provide several pioneer examples on infection-induced host gene reprogramming (Bhavsar et al., 2007).

2. Conclusion

The regulation of complex eukaryote genomes entails not only sequence-specific DNA-binding factors, but also additional levels of regulation such as DNA modifications, histone post-translational modifications and chromatin remodeling. These modifications are often referred to as being epigenetic although some of them have not been shown to fulfill the strict definition of epigenetics, which implies heritability through mitosis or meiosis (Berger et al., 2009). During development and cellular differentiation, these epigenetic marks undergo dynamic changes that ultimately contribute to produce and maintain distinct cell types of an organism (Meissner, 2010). Elucidating how these epigenetic marks participate in the regulation of cellular identity is crucial to better understand embryonic development and etiology of many diseases. The ability of microbes to epigenetically influence host gene expression plays a major role in the pathogenesis of chronic diseases. Similarly, although the mechanisms are less well understood, the idea of epigenetic changes in hostcells associated with chronic microbial infections (e.g. *H. pylori*) contributing to disease is conceptually satisfying. What is less obvious is the significance of such heritable changes in host cell behavior during acute pathogen mediated disease. Perhaps a unifying theme is the modulation of the immune response, inflammation and intracellular host defenses. This requires further exploration. Although a lot of research has been done in the field of epigenetics, there remain active challenges and questions to be answered.

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